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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/982,284	12/01/1997	HENRYK LUBON	030523/0141	9099

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/982,284	LUBON ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-30&10-31-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Prosecution Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-30-03 has been entered.

The amendment filed 10-30-03 was not been entered because it was not in the proper format (claims 1-74 were excluded from the amendment).

The amendment filed 10-31-03 has been entered.

The arguments filed 10-30-03 and 10-31-03 are duplicates. Applicant's arguments filed therein have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 101-110 have been added. Claims 75-110 are pending and under consideration in the instant application.

The title of the application should be changed to more closely reflect the claimed invention.

Reference to journal articles using A12, A50, etc. in the arguments filed 10-31-03 is confusing. For example, reference to Zbikowska on pg 11, line 7, of the response states A22 and A23. However, A22 and A23 are Krisher and Lacombe, respectively, in the IDS filed 8-30-99, while A22 and A23 are both by Zbikowska in the IDS filed 10-30-03.

The effective filing date of the instant invention is 12-1-97.

Claim Objections

There should be a comma after "a uropontin/osteopontin gene" in claims 75, 80, 83, 88, 93, 96.

There should be a comma after "bone morphogenetic protein" in claims 86 and 99.

The independent claims should be clarified. Describing the 5' regulatory sequences at the end of the claim instead of in step a) where the 5' regulatory sequences are first mention is confusing. Using language describing both the "5' regulatory region" and the "promoter" together in the same claim is confusing. If both terms are required, it is noted that the claims as written do not reflect the essence of the invention which is using a 5' regulatory region that has a uromodulin, rennin, erythorpoietin, apolipoprotein E, uropontin/osteopontin or aquaporin promoter because only the 5' regulatory sequence must be from a uromodulin, rennin, erythorpoietin,

apolipoprotein E, uropontin/osteopontin or aquaporin gene. As an example, claim 75 would be clearer if written as follows:

A method of producing a protein or peptide in the urine of a non-human transgenic mammal comprising:

a) providing a non-human transgenic mammal having stably integrated into its genome a nucleic acid sequence encoding a protein or peptide operably linked to a uromodulin, rennin, erythorpoietin, apolipoprotein E, uropontin/osteopontin or aquaporin promoter; and

b) allowing the protein to be expressed and secreted into the urine of the mammal.

Claim Rejections - 35 USC ' 112

Claims 75-100 remain rejected and claims 101-110 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

5' Regulatory sequences that cause exogenous protein secretion into the urine of a transgenic mammal

The claims are currently limited to a method making a protein in the urine of a transgenic non-human mammal using a nucleic acid sequence encoding a protein operably linked to a 5' regulatory sequence comprising a promoter, wherein the 5' regulatory sequence is from a uromodulin, renin, erythropoietin, apolipoprotein E (ApoE), uropontin/osteopontin or aquaporin gene. The preamble requires producing a protein in the urine of the mammal, which is given weight under enablement because each limitation must be enabled. For protein to be produced in the urine of a transgenic mammal, expression of the exogenous gene and secretion of the exogenous protein into the urine of a transgenic mammal must occur.

Overall, it was unpredictable at the time of filing what effect a promoter would have on the phenotype of transgenic animals (Strojek, Houdebine, Wall and Kappel all of record).

WAP and uroplakin 5' regulatory regions capable of producing exogenous protein in the urine of a transgenic mammal

Lubon of record taught the WAP promoter allowed secretion of protein into the milk and urine of the transgenic mice and isolating the protein from the milk or urine (US Patent 5,880,327, March 9, 1999; col. 6, lines 45-52; col. 9, line 19). Sun of record taught the uroplakin promoter allowed secretion of protein into the urine of transgenic mice and using the bladder of the mice as a bioreactor for isolating the protein from the

urine (WO 96/39494, Dec. 12, 1996; US Patent 5,824,543, Oct. 20, 1998; pg 8, lines 3-12; pg 9, lines 15-36; pg 10, line 4; ¶ bridging col. 5 and 6, col. 6, line 55, Example 2). The specification taught making transgenic mice and pigs whose genomes' comprised a sequence encoding human protein C (HPC) operatively linked to the WAP promoter, wherein said mice and pigs expressed HPC in their urine (¶ bridging pg 38-39). Thus, the specification provides adequate written description for the WAP and uroplakin promoters as being capable of secreting exogenous proteins into the urine of transgenic mammals.

While 5' regulatory regions capable of producing exogenous proteins in the urine of transgenic mammals were known in the art, neither the specification nor the art at the time of filing taught that detecting exogenous protein in the kidney or bladder of a transgenic meant that the exogenous protein was secreted into the urine of the transgenic. Obtaining exogenous protein expression in the kidneys, urinary tract or reproductive tract does not correlate to producing the exogenous protein in the urine as claimed because expression does not guarantee the protein is secreted out of the cell and into the urine. The exogenous protein may be expressed within a kidney or urinary tract cell, but the protein not have the proper signal sequence required to be secreted out of the cell, specifically into the urine. The proper 5' regulatory region with adequate signal sequences that provide secretion into the urine must be in the transgene and control expression of the exogenous gene.

Uromodulin

Zbikowska (Biochem. J. 2002. Vol. 365. pg 7-11) taught using a 6.72 kb fragment of the uromodulin gene comprising the promoter and exons 1 and 2 to make mice that secreted exogenous proteins into their urine (pg 8, Fig. 1). Thus, the uromodulin gene fragment comprising the promoter and exons 1 and 2 was essential to obtaining secretion of exogenous protein into the urine. The specification suggests using a uromodulin promoter to express proteins in the kidney or bladder (pg 29, lines 26-27). The specification teaches isolating the human uromodulin promoter (pg 41, Example 2) and making a construct for expression in the urinary tract with a uromodulin promoter (pg 42, Example 3). The specification does not provide adequate written description for using a uromodulin 5' region to secrete an exogenous protein into the urine of a transgenic mammal because it does not teach that which is essential – the uromodulin gene fragment comprising the promoter and exons 1 and 2. While the human, rat and cow uromodulin promoters were described in Yu (1994, Gene Expr., Vol. 4, pg 63-75), Yu did not teach the gene fragment that was essential to secrete exogenous proteins into the urine of transgenic mammals. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to uromodulin promoters. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to uromodulin regulatory regions. Therefore, the specification does

not provide adequate description of the uromodulin 5' regulatory region that caused protein secretion into the urine of transgenic animals as claimed.

Apolipoprotein E

Simonet (1990, J. Biol. Chem., Vol. 265, pages 10809-10812) taught transgenic mice whose genomes' comprise a transgene encoding a protein operatively linked to the apolipoprotein E promoter wherein expression of the protein occurs in the kidney (pg 10810, ¶ bridging col. 1-2) but did not teach mice secrete the protein into their urine. The specification suggests using an apoE promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder. The specification suggests making a construct for expression in the urinary tract with an ApoE promoter (pg 42, Example 3). The specification does not provide adequate written description for the apolipoprotein E 5' region required to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to an ApoE promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to ApoE regulatory regions. The teachings in the specification are, in fact, less than the teachings of Simone, who actually reduced the mouse to practice and did not teach obtaining secretion of exogenous protein into the urine. Therefore, the specification did not provide adequate description of the ApoE 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Renin

Fukamizu (Biochem. Biophys. Res. Comm., 1994, Vol. 199, pg 183-190) taught a mouse whose genome comprised a nucleic acid sequence comprising the chloramphenicol acetyl transferase (CAT) gene operably linked to a renin 5' regulatory region but did not teach the mouse secreted CAT into its urine. While the specification suggests using a renin promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder, and one of skill could make a transgenic with a construct with the renin promoter, the specification does not provide adequate written description for the renin 5' regulatory region required to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to a renin promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to renin regulatory regions. The teachings in the specification are, in fact, less than the teachings of Fukamizu, who actually reduced the mouse to practice and did not teach obtaining secretion of exogenous protein into the urine. Therefore, the specification did not provide adequate description of the renin 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Since the time of filing, Germain (2001, Clin. Exp Pharm. Vol. 28, pg 1056-1059) taught using a rennin promoter to obtain protein expression in the kidney. However, the promoter was not known until 1998 (see pg 1056, col. 2, last sentence, reference 9,

Germain). More importantly, Germain (2001) did not teach the rennin promoter caused secretion of the exogenous protein into the urine. Obtaining exogenous protein expression in the kidneys, urinary tract or reproductive tract is not adequate to show that secretion of the protein out of the cell and into the urine will occur. In the case of Germain (2001), the exogenous protein may have been expressed within the cells of the kidney without being secreted outside of the cells and into the urine because the 5' regulatory region did not have the proper signal sequence required for secretion out of the cell, specifically into the urine.

Erythropoietin

Semenza (Annals NY Acad. Sci., 1994, Vol. 718, pg 41-49) taught a mouse whose genome comprised a nucleic acid sequence comprising the human erythropoietin gene, including the 5' and 3' regulatory regions. The protein was detected in the kidneys of the mice (pg 42, 2nd full ¶, Fig. 1, "Ki"). Haidar (J. Structural Biol. April 1997, Vol. 118, pg 220-225) taught a mouse whose genome comprised a nucleic acid sequence comprising the lacZ gene operably linked to the 5' and 3' erythropoietin regulatory region. The protein was detected in the kidneys of the mice (pg 222, last line). While the specification suggests using an Epo promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder, and one of skill could make a transgenic with a construct comprising the Epo promoter, the specification does not provide adequate written description for the Epo 5' regulatory region required

to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to an Epo promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to Epo regulatory regions. The teachings in the specification are, in fact, less than the teachings of Semenza, who actually reduced the mouse to practice and did not teach obtaining secretion of exogenous protein into the urine. Therefore, the specification did not provide adequate description of the Epo 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Uropontin/osteopontin and aquaporin

While the specification suggests using a uropontin/osteopontin promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder, and one of skill could make a transgenic with a construct comprising the uropontin/osteopontin or aquaporin promoter, the specification does not provide adequate written description for the uropontin/osteopontin or aquaporin 5' regulatory regions required to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to a uropontin/osteopontin or aquaporin promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to uropontin/osteopontin or aquaporin regulatory regions. Therefore, the specification did

not provide adequate description of the uropontin/osteopontin or aquaporin 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Since the time of filing Nelson (1998, Am J Physiol. Vol. 275. pg C216-226), Zharkikh (2002, Am J Physiol Renal Physiol. Vol. 283, pg F1351-1364) and Stricklett (1999, Exp Nephrol. Vol. 7, pg 67-74) made transgenic mammals comprising a nucleic acid sequence encoding a protein operably linked to an aquaporin 5' regulatory region; however, the fragment of the aquaporin 5' regulatory region used by Nelson, Zharkikh and Stricklett was not taught in the specification as originally filed. Nelson (1998) taught using a 14 kb 5' flanking region of the aquaporin 2 gene and references Hozawa (1996, Am Physiol Soc. Pg C1695-1702); however, Hozawa taught the aquaporin 2 promoter was variable (9 or 14 kb). One of ordinary skill would not have known to choose the 14 kb aquaporin 2 promoter of Hozawa. More importantly, Nelson, Zharkhik and Stricklett did not teach the aquaporin promoter caused secretion of the exogenous protein into the urine. Obtaining exogenous protein expression in the kidneys, urinary tract or reproductive tract is not adequate to show that secretion of the protein out of the cell and into the urine occurred. In the case of Nelson, Zharkhik and Stricklett, the exogenous protein may have been expressed within the cell without being secreted outside of the cell and into the urine because the 5' regulatory region did not have the

proper signal sequence required to cause secretion out of the cell, specifically into the urine.

Likewise, Sakuma (2003, J Orthop Sci. Vol. 8, pg 361-366) made transgenic mammals comprising a nucleic acid sequence encoding a protein operably linked to a osteopontin 5' regulatory region; however, the fragment of the osteopontin 5' regulatory region used by Sakuma was not known in the art or taught in the specification as originally filed. The osteopontin 5' regulatory region used by Sakuma was not available until 1998 (see pg 361, col. 2, "Production of Transgenic mice" reference 20; Sato). Applicants refer to Jiang (1998) in the arguments on pg 13 of the response filed 10-30-03; however, Jiang did not teach a transgenic mammal as claimed.

Overall, an adequate written description of a uromodulin, renin, Epo, apoE, uropontin/osteopontin or aquaporin 5' regulatory regions capable of secreting exogenous protein into the urine of a transgenic mammal requires more than a mere statement that it is part of the invention. It is not sufficient to state 5' regulatory regions from uromodulin, renin, erythropoietin, apoE, uropontin/osteopontin or aquaporin genes are capable of secreting exogenous protein into the urine of transgenic mammals. A mere suggestion to use such 5' regulatory regions to secrete exogenous proteins into the urine of transgenic mammals in view of the unpredictability in the art of promoter function in transgenics is simply a wish to know whether such 5' regulatory regions have

that capability. Thus, claiming a method of producing a protein in the urine of a mammal using any 5' regulatory region of the uromodulin, renin, erythropoietin, apoE, uropontin/osteopontin or aquaporin gene without defining the specific structure of the promoter that has that function is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In conclusion, the 5' regulatory sequences should be limited to the WAP promoter, the uroplakin promoter or promoters that cause secretion of exogenous protein into the urine of the transgenic mammal. Using Epo, ApoE, aquaporin, rennin, osteopontin or uromodulin 5' regulatory regions to cause secretion of exogenous proteins into the urine of transgenic mammals as claimed is not enabled.

Applicants argue the specification discloses using the 5' regulatory sequences as claimed, and that such 5' regulatory regions are isolated from genes known to be associated with urinary tract tissue (pg 8-9 of response filed 10-31-03). Therefore, applicants argue the specification provides adequate written description of the 5' regulatory sequences claimed. Applicants' argument is not persuasive.

Listing possible 5' regulatory sequences having a possible function is not adequate written description. It is merely a wish to know such sequences. The art taught making the some of the mice encompassed by the claims, but the art did not

expressly teach the mice secreted the protein in their urine. Nor do applicants show that the mice known in the art expressed exogenous protein in their urine. It was not predictable which 5' regulatory regions provided secretion of exogenous proteins into the urine of transgenic mammals for reasons of record, and a mere list of possible promoters that provide such function is inadequate to overcome such unpredictability. The specification does not provide any correlation between the 5' regions in the claims and those known to cause exogenous protein production in the urine of transgenic mammals. The specification does not teach an assay to determine the parts of the uromodulin, renin, erythropoietin, ApoE, osteopontin/uropontin or aquaporin 5' regulatory regions having the desired function. The level of expression obtained using the 5' regulatory sequences claimed may be inadequate to obtain detectable levels of protein in the urine, the promoter may not function as expected in the transgenic and the tissue-specificity within the urinary tract may not be adequate to allow secretion into the urine. Therefore, the specification does not provide adequate written description for 5' regulatory sequences claimed that provide expression of exogenous protein in the urine of transgenic non-human mammals.

In addition, the specification and the art do not provide adequate written description for any uromodulin, rennin, Epo, ApoE, osteopontin or aquaporin gene as broadly claimed. I.e. "a" uromodulin gene lacks written description because one uromodulin gene does not describe all uromodulin genes.

Applicants argue the declaration by Dr. Serguei Soukharev teaches obtaining protein expression in the urine of a transgenic mammal using the uromodulin promoter (pg 9 of response filed 10-31-03). Therefore, applicants conclude the specification provides adequate written description for the 5' regulatory region of the uromodulin gene that produces exogenous protein in the urine of transgenic mammals. Applicants' argument is not persuasive because the transgenic mammal was made using a construct comprising exons 1 and 2 (and it appears an intron) of the uromodulin 5' regulatory region, which was not described in the specification or the art at the time of filing and is considered essential to the invention (see Exhibit 2A attached to the declaration filed 11-5-01). In fact, the declaration does not fully disclose what portion of the uromodulin 5' regulatory region was used because it says "only part of uromodulin promoter is shown" (see caption of Exhibit 2A). Therefore, the declaration does not correlate to the specification as originally filed because it contains information that was not known at the time of filing or disclosed in the specification as originally filed. In addition, the declaration does not describe the structure of the uromodulin promoter required to produce exogenous protein in the urine of a transgenic mammal, which is essential to the invention.

3' Regulatory sequences that cause exogenous protein secretion into the urine of a transgenic mammal

The specification does not provide adequate written description of any 3' urinary tract-specific regulatory sequences that provide expression of a protein in the urine (claims 79, 82, 92 and 95). While the 3' region of WAP gene was used in the construct of Sympson (pg 683, col. 2, line 3), Sympson did not teach the 3' region of the WAP gene was urinary-tract specific or provide expression of the protein in the urine. Neither the specification nor the art at the time of filing teach a 3' urinary tract-specific regulatory sequence that provides expression of a protein in the urine. Therefore, such regulatory sequences lack written description.

Applicants have not provided any specific arguments regarding 3' regulatory sequences that cause expression of exogenous proteins in the urine of transgenic mammals. No 3' regulatory region of the uromodulin, rennin, Epo, ApoE, uropontin/osteopontin or aquaporin gene was known to cause expression of exogenous proteins in the urine of transgenic mammals in and of itself.

Producing enzymes in the urine of a transgenic mammal

The specification does not provide adequate written description for any transgenics that express enzymes in their urine (claims 84, 85, 97 and 98). While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic

mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-carboxylase, in the urine. Thus, the specification does not provide adequate written description that the combination of elements described have the desired function, i.e. the transgenics express functional enzyme in their urine or the enzyme alters the phenotype of the transgenic. Applicants argue the amendment overcomes this rejection. Applicants' argument is not persuasive because claims 84, 95, 97 and 98 require expressing enzymes in the urine.

Claims 75-100 remain rejected and claims 101-110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammal whose genome comprises a transgene comprising a nucleic acid sequence encoding a protein operatively linked to a promoter that causes secretion of the protein into the urine of the transgenic mammal, wherein said protein is expressed and secreted into the urine of said transgenic non-human mammal and a method of producing a protein in the urine of said non-human mammal, does not reasonably provide enablement for using 5' regulatory sequences of the uromodulin, renin, erythropoietin, apolipoprotein E, uropontin/osteopontin or aquaporin genes to obtain expression or secretion of exogenous protein in the urine of transgenic non-human mammals, using any 3' regulatory sequences to obtain exogenous protein

expression in the urine, or expressing an enzyme in the urine of transgenic non-human mammals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record. Applicants' arguments have been addressed above.

The claims are not enabled because the 5' regulatory regions that provide secretion of a protein in the urine of the transgenic mammal are not adequately taught for the reasons set forth above in the written description rejection. Applicants' arguments have been addressed above in the written description rejection.

Claims 87 and 100 are not enabled because the specification does not provide adequate guidance for one of skill to make transgenic pigs, sheep, goats, cows, rabbits, or horses. ES cells that provide germline transmission in species other than mice had not been obtained. Furthermore, the parameters required to obtain germline transmission of an exogenous transgene differ between mammalian species for reasons of record. The art at the time the invention was made did not teach how to make a transgenic pig, sheep, goat, cow, rabbit or horse or how to obtain pig, sheep, goat, cow, rabbit or horse ES cells (claims 87 and 100). Therefore, it was unpredictable how to make such transgenic animals at the time the invention was made. The specification does not teach how to make a transgenic pig, sheep, goat, cow, rabbit or horse or how to obtain pig, sheep, goat, cow, rabbit or horse ES cells. Thus, it would have required

one of skill undue experimentation to determine how to make a transgenic pig, sheep, goat, cow, rabbit or horse as claimed.

Applicants have not addressed this issue.

The specification does not enable expressing enzymes in the urine of transgenic mammals (claims 84, 85, 97 and 98). The disclosed purpose of expressing enzymes in the urine of animals is to degrade/detoxify feces, urine, microbes or chemical pollutants. Sympson of record taught expressing stromelysin-1 (which degrades collagen) in transgenic mice and D'Armiento of record taught that transgenic mice expressing MMP (which also degrades collagen) do not survive (page 5734, col. 2, line 6). While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-carboxylase, in the urine. Given the purpose of the specification taken with the teachings in the specification and in the art, the specification does not enable expressing enzymes in the urine of a transgenic non-human animal.

Applicants have not addressed this issue.

Claims 75-100 remain rejected and claims 101-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 75 and 88 remain indefinite because they do not clearly set for the regulatory sequences. 75 (a) refers to "expression regulatory sequences" but b) refers to "5' regulatory sequences." The structure of the transgene is not clearly set forth. The wording in a) is confusing. The wording after b) referring to the regulatory sequence in a) is confusing. The phrase "5' regulatory sequences, comprising a promoter, wherein said 5' regulatory sequences are selected from the group consisting of a 5' regulatory sequence of a uromodulin gene..." does not make sense. Describing step a) as – providing a non-human transgenic mammal having a genome comprising a nucleic acid sequence encoding a protein operably linked to a promoter, wherein the promoter is selected from the group consisting of a uromodulin promoter, a renin promoter...-- would be clear.

The rejection of claims 80, 83, 93 and 96 has been withdrawn because the phrase "3' regulatory sequences selected from a group consisting of a uromodulin gene..." has been changed to "3' regulatory sequences selected from a group consisting of a 3' regulatory sequence of a uromodulin gene...."

The phrase "uropontin/osteopontin" is unclear (75, 88). It is unclear if one gene has two names or if two genes are being clumped together.

The phrase "urine containing said protein or peptide" in claims 76, 89 lacks antecedent basis in claim 75.

Reference to the 5' regulatory sequence in claims 77, 90, 101-110 when limiting the promoter of claim 75 or 88 is unclear. --The method of claim 75, wherein the promoter is a uromodulin promoter—would overcome this rejection.

The phrase "operably linked to said exogenous gene" in claims 78, 81, 91, 94 is redundant because the expression regulatory sequences in claim 75 or 88 are already operably linked to the exogenous gene.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

> by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 75, 78, 79, 81, 82, 84, 87-89, 91, 92, 94, 95, 97, 100, 101 and 106 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukamizu (Biochem. Biophys. Res. Comm., 1994, Vol. 199, pg 183-190).

Fukamizu taught a mouse whose genome comprised a nucleic acid sequence comprising the chloramphenicol acetyl transferase (CAT) gene operably linked to a renin 5' regulatory region. The mice inherently secreted CAT protein into their urine because the protein was detected in the kidneys of the mice (pg 188, Fig. 4B, Lane 4-6, see caption). According to applicants' arguments filed 10-30-03, expressing exogenous protein in the kidney is an indication that the exogenous protein will be secreted into the urine of transgenic mammals (see arguments for Epo on pg 13 of response which states "The current invention teaches that these hormones would be secreted into

urine."). The product of Fukamizu is no different than the product claimed because it expresses CAT in the kidney and inherently secretes CAT into the urine.

Claims 75, 78-83, 87-89, 91-96, 100, 102 and 107 are rejected under 35 U.S.C. 102(b) as being anticipated by Semenza (Annals NY Acad. Sci., 1994, Vol. 718, pg 41-49).

Semenza taught a mouse whose genome comprised a nucleic acid sequence comprising the human erythropoietin gene, including the 5' and 3' regulatory regions. The mice inherently secreted human erythropoietin protein into their urine because the protein was detected in the kidneys of the mice (pg 42, 2nd full ¶, Fig. 1, "Ki").

Claims 75, 78-83, 87-89, 91-96, 100, 102 and 107 are rejected under 35 U.S.C. 102(a) as being anticipated by Haidar (J. Structural Biol. April 1997, Vol. 118, pg 220-225).

Haidar taught a mouse whose genome comprised a nucleic acid sequence comprising the lacZ gene operably linked to the 5' and 3' erythropoietin regulatory region. The mice inherently secreted LacZ into their urine because the protein was detected in the kidneys of the mice (pg 222, last line).

Claims 75, 78-83, 87-89, 91-6, 100, 103 and 108 are rejected under 35 U.S.C. 102(b) as being anticipated by Simonet (J. Biological Chem., 1990, Vol. 265, pg 10809-10812).

Simonet taught a mouse whose genome comprised a nucleic acid sequence comprising the human apolipoprotein E gene, including the 5' and 3' regulatory regions. The mice inherently secreted human apoE protein into their urine because the protein was detected in the kidneys of the mice.

Claims 75, 78-82, 86-89, 91, 92, 94, 95, 99, 100, 103 and 108 are rejected under 35 U.S.C. 102(e) as being anticipated by Boyle (US Patent 6,613,544, Sept. 2, 2003).

Boyle taught a mouse whose genome comprised a nucleic acid sequence comprising the osteoprotegerin coding region operably linked to the apoE promoter. The mice inherently secreted osteoprotegerin into their urine because apoE promoter was found to cause secretion of proteins into the urine. Claims 86 and 99 are included because osteoprotegerin is a growth factor of the TNF family.

Conclusion

No claim is allowed.

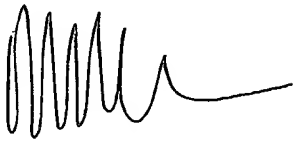
Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER